REMARKS

Amendments to the Specification

Applicants have amended the specification to reflect the amendments to the drawings. Specifically, applicants have replaced the words "Figure 13-1" and "Figure 13-2" with "Figure 13A" and "Figure 13B," respectively, in the specification.

As requested by the Examiner, applicants also submit herewith a substitute copy of the specification pages 1-115 as originally filed.

Amendments to the Claims

Applicants have amended claim 69 to improve its form by replacing "comprises" with "is."

Applicants have amended claims 70, 73, 76 and 79 to further recite that the claimed antibodies specifically bind to an APRIL polypeptide.

Applicants have added claims 95-97. Added claim 95 is directed to an anti-APRIL monoclonal antibody that competitively inhibits the binding of the 3C6.4.2 antibody to APRIL. Added claim 96 is directed to an anti-APRIL monoclonal antibody that competitively inhibits the binding of the 5E11.1.2 antibody to APRIL. Support for added claims 95-96 can be found, *inter alia*, on page 65, line 39 to page 66, line 4 and Example 9 in the specification as originally filed.

Applicants have also added claim 97 directed to a method for inhibiting or neutralizing APRIL polypeptide biological activity in mammalian cells, comprising exposing said mammalian cells to an effective amount of an anti-APRIL antibody according to any one of claims 67-74, 81-82, 85-86 and 95-96. Support for this amendment can be found thoroughout the specification, e.g., in claims 19 and 32-33 as originally filed.

Amendments to the Drawings

Applicants have submited an entire set of substitute drawings containing the changes as requested in the Notice of Draftsperson's Patent Drawing Review attached to the June 2, 2003 Office Action.

Restriction and Election Requirements

The Examiner has maintained his restriction of method claims 92-94 and antibody claims of Group XXXV (claims 67-91). As discussed above, applicants have added claims 95-96 directed to anti-APRIL antibodies of this invention. Applicants respectfully request that the Examiner examine added claims 95-96 with Group XXXV claims. In the event that the Examiner disagrees, applicants maintain their provisional election of claims 67-91 of Group XXXV.

Applicants have also added claim 97 directed to a method of using the claimed anti-APRIL antibodies. Claims 92-94 and added claim 97, which depend from the claims in Group XXXV, remain pending for consideration for rejoinder with Group XXXV in the event that the antibodies of Group XXXV are deemed allowable. MPEP 821.04.

Priority

The present application claims benefit from two United States provisional applications 60/182,938, filed February 16, 2000 and 60/226,986, filed August 22, 2000. *See* lines 5-8 of page 1 of the specification as originally filed. Applicants request that the Examiner acknowledge the claims for priority under 35 U.S.C. 119(e).

Rejection Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 69, 81-88 and 90-91 under 35 U.S.C. § 112, second paragraph for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner states that claim 69 is indefinite because it recites the word "comprises." Applicants have amended claim 69 as suggested by the Examiner by replacing the word "comprises" with "is."

The Examiner states that claims 81-88 are indefinite because the phrase "a sequence derived from" renders the metes and bounds of said "chimeric" antibody unclear and ambiguous. Applicants disagree.

The specification as filed states that "chimeric" monoclonal antibodies specifically include antibodies having a portion of the heavy and/or light chain identical with or

homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity. *See* page 42, lines 16-27 of the specification as originally filed. Thus, the phrase "sequence derived from" further defines the claimed chimeric antibody and provides a reference to a particular antibody from which a portion of the chimeric antibody has been derived.

Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 70, 73, 76, 79 and 89 under 35 U.S.C. § 112, first paragraph, because, allegedly, while the specification is enabling for antibody which specifically binds SEQ ID NO:8 and specifically disclosed monoclonal antibodies (3C6.4.2, 5E11.1.2, 5G8.2.2 and 5E8.7.4), it is not enabling for any monoclonal antibody which binds to "the same epitope as the epitope" to which the specifically disclosed monoclonal antibodies bind. The Examiner specifically states that detailed information is lacking regarding specific epitopes recognized by the specifically disclosed antibodies and whether those antibodies would function in blocking APRIL binding to TACI and BCMA. The Examiner concludes that it would take an undue amount of experimentation for one skilled in the art to practice the invention as claimed. Applicants disagree.

The specification as filed provides the proper guidance. The application states that epitope binding properties can be determined, e.g., by a competitive inhibition binding assay (e.g., page 65, line 39 to page 66, line 8 of the specification as originally filed). In a competitive binding assay, an anti-April antibody of interest would competitively inhibit the binding of a specifically disclosed monoclonal antibody to APRIL (e.g., page 66, lines 2 to 4 of the specification as originally filed). Example 9 of the specification provides details regarding a useful and simple competitive binding ELISA assay according to this invention and demonstrates the use of the assay with the specifically disclosed antibodies. Example 8 of the specification discloses a binding assay useful for testing the blocking activity of anti-APRIL antibodies on the interaction between APRIL and TACI or APRIL and BCMA and

demonstrates the use of the blocking assay with the specifically disclosed antibodies. Thus, one of ordinary skill in the art could easily determine whether other antibodies bound to the same epitope of any one of the specifically disclosed antibodies. Thus, the antibodies of amended claims 70, 73, 76, 79 and 89 are enabled.

The Examiner has also rejected claims 70, 73, 76, 79 and 89 under 35 U.S.C. § 112, first paragraph for allegedly containing subject matter that is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, while the Examiner acknowledges that the applicants had possession of an antibody of 3C6.4.2, 5E11.1.2, 5G8.2.2, and 5E8.7.4, he states that applicants were not in possession of any monoclonal antibody which binds to "the same epitope[s] as the epitope[s]" to which the 3C6.4.2, 5E11.1.2, 5G8.2.2, and 5E8.7.4 antibodies bind. Applicants disagree.

Possession may be shown in variety of ways including by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. Fed. Reg. 66(4):1104, col. 3, lines 45-56, January 5, 2001. Amended claims 70, 73, 76 and 79 representatively describe an object having both structural and functional characteristics - - an antibody which has the functional characteristics of specifically binding to an APRIL polypeptide and an epitope recognized by an antibody specifically disclosed in the application.

The written description guidelines make clear that a "representative number of species" is not required for a genus claim. Fed. Reg. 66(4):1106, col. 3, lines 37-39, January 5, 2001. The guidelines indicate that the need for a disclosure of a representative number is balanced against the skill and knowledge in the art. Fed. Reg. 66(4):1106, col. 3, lines 39-42. Applicants have specifically disclosed, deposited, and tested a plurality of antibodies (e.g., Examples 8 and 9 of the specification). The specification teaches and demonstrates that antibodies that bind to the epitopes described in this invention can easily be determined by performing competitive binding assays using a APRIL polypeptide and the antibodies specifically disclosed and deposited (e.g., page 65, line 39 to page 66, line 8 and Example 9 of the specification as filed). One of ordinary skill in the art would immediately recognize that applicants were in possession of the necessary common attributes or features of the elements possessed by the members of the genera. Thus, the antibodies of amended claims 70, 73, 76, 79 and 89 are adequately described.

Rejection Under 35 U.S.C. § 102(b)

The Examiner has rejected claims 67-68 and 89 under 35 U.S.C. § 102(b) as being anticipated by WO/9900518 ("the '518 publication"), as is evidenced by the specification on page 10, lines 12-15 and Bost et al. Specifically, the Examiner states that the '518 publication teaches a monoclonal antibody that binds to APRIL and that the antibodies of claims 67-68 and 89 are the same as the monoclonal antibody of the '518 publication (page 6, third full paragraph of the June 2003 Office Action). The Examiner acknowledges that the '518 publication does not teach antibodies that block APRIL binding to a TACI receptor or a BCMA receptor, but he considers the binding of APRIL to a TACI receptor or a BCMA receptor to be an "inherent property" of the antibodies of the '518 publication. Applicants traverse.

The Examiner refers to page 5, lines 32-35 of the '518 publication, which portion generally refers to antibodies that specifically bind to an epitope of TNF-gamma. No polyclonal antibodies were made or tested in the '518 publication. No specific monoclonal antibodies were made or tested in the '518 publication. Furthermore, no receptors were identified for the TNF-gamma protein in the '518 publication.

To anticipate a claim, the reference must teach each and every element of the claim. MPEP 2131. Claims 67-68 and claim 89 as it depends therefrom in part are directed to monoclonal antibodies that specifically bind to an APRIL polypeptide and block the binding of said APRIL polypeptide to a TACI receptor and/or a BCMA receptor. Nowhere does the '518 publication specifically teach monoclonal antibodies that block TACI or BCMA binding to APRIL. The Examiner admits that the '518 publication is silent as to the blocking of an APRIL polypeptide to a TACI receptor or a BCMA receptor (page 6, sixth full paragraph of the June 2003 Office Action). Therefore, it is clear that recitation of those elements are missing from the '518 publication.

The Examiner states that the blocking of binding of said APRIL polypeptide to a TACI receptor or a BCMA receptor is considered "an inherent property" and that it is applicants' "burden to show that the reference antibody does not bind to SEQ ID NO:2 recited in the claim" (page 6, sixth full paragraph and page 6, last paragraph, respectively, of the June 2003 Office Action). The Examiner is mistaken.

First, an antibody that blocks TACI and/or BCMA binding to APRIL would not have been envisaged by one of skill in the art prior to this invention. To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. MPEP 2112. Applicants believe that the instant application is the first identification of any receptor for APRIL. The present application describes TACI and BCMA as receptors for APRIL and the discovery that TACI and BCMA can be activated directly through APRIL binding (e.g., Example 4 of the specification). As discussed above, the '518 publication provides none of this disclosure.

Second, the claimed blocking ability of the anti-APRIL antibodies of claims 67-68 is not an "inherent property" of all antibodies that bind APRIL. In relying upon the theory of inherency, the Examiner must provide "a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." MPEP 2112. An antibody that is reactive against a part of APRIL that does not bind TACI or BCMA may not block the binding of TACI or BCMA to APRIL. The '518 publication, without providing specific antibodies, only

generally refers to antibodies that bind APRIL. The '518 publication cannot distinguish between antibodies that block APRIL binding to TACI and/or BCMA because it does not identify any receptor for APRIL. Thus, the Examiner has not shown that the alleged "inherent property" necessarily flows from the teachings of the '518 publication. Applicants do not believe that a basis for inherency has been established.

Third, claims 67-68 and relevant parts of claim 89 depending therefrom are not directed to all antibodies that bind APRIL, rather they are directed to a specific set of monoclonal antibodies against APRIL that have special properties and characteristics that are not described in the '518 publication and are not of the same scope as the antibodies described in the '518 publication. Thus, a rejection based on inherent anticipation is not proper.

Finally, contrary to the Examiner's assertions, applicants have no burden to show that the antibodies of the '518 publication do not bind to APRIL because (1) the '518 publication does not inherently anticipate claims 67-68 and 89 for the above reasons and because (2) antibodies that generally bind APRIL are not the subject matter of the claims at issue.

In view of the foregoing, claims 67-68 and claim 89 are not anticipated by the '518 publication.

Rejection Under 35 U.S.C. § 102(e)

The Examiner has rejected claims 67 and 68 for being anticipated by United States Patent No. 6,440,694 (the '694 patent) under 35 U.S.C. § 102(e). Specifically, the Examiner states that the antibodies that are described on column 3, lines 48-54 of the '694 patent are the same as the antibodies of claims 67-68. The Examiner acknowledges that the '694 patent does not teach antibodies that block APRIL binding to a TACI receptor or a BCMA receptor, but he considers that the blockage of the binding of APRIL to a TACI receptor or a BCMA receptor as an "inherent property" of the antibodies of the '694 patent. Applicants traverse.

The '694 patent generally refers to polyclonal and monoclonal antibodies against polypeptides, TRDL-11 (SEQ ID NO:2) and TRDL-14 (SEQ ID NO:4), that share some

sequence similarities with full-length APRIL. The TRDL-11 sequence differs with the C-terminus with APRIL such that it is shorter. The TRDL-14 sequence differs with a mid-portion of APRIL such that at least residues 111-127 of APRIL are missing. No polyclonal antibodies were made or tested in the '694 patent. No specific monoclonal antibodies were made or tested in the '694 patent. Furthermore, no receptors were identified for any TRDL polypeptide in the '694 patent.

To anticipate a claim, the reference must teach each and every element of the claim. MPEP 2131. Claims 67-68 are directed to monoclonal antibodies that specifically bind to an APRIL polypeptide and block the binding of said APRIL polypeptide to a TACI receptor and/or a BCMA receptor. Nowhere does the '694 patent teach or describe monoclonal antibodies that block TACI or BCMA binding to APRIL. The Examiner admits that the '694 patent is silent as to the blocking of the binding of an APRIL polypeptide to a TACI receptor or a BCMA receptor (page 8, second full paragraph of the June 2003 Office Action). Therefore, it is clear that recitation of those elements are missing from the '694 patent.

The Examiner considers the blockage of binding of said APRIL polypeptide to a TACI receptor or a BCMA receptor to be "an inherent property" of an antibody of the '694 patent and that it is applicants' "burden to show that the reference antibody does not bind to SEQ ID NO:2 recited in the claim" (page 8, second full paragraph and page 8, third full paragraph, respectively, of the June 2003 Office Action). Again, the Examiner is mistaken.

First, an antibody that blocks TACI and/or BCMA binding to APRIL would not have been envisaged by one of skill in the art prior to this invention. To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. MPEP 2112. As discussed above, applicants believe that the instant application is the first identification of any receptor for APRIL. The present application describes TACI and BCMA as receptors for APRIL and the discovery that TACI and BCMA can be activated directly through APRIL binding (e.g., Example 4 of the specification). The '694 patent provides none of this disclosure.

Second, the claimed blocking ability of the anti-APRIL antibodies of claims 67-68 is not an "inherent property" of all antibodies that bind APRIL. In relying upon the theory of

inherency, the Examiner must provide "a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." MPEP 2112. An antibody that is reactive against a part of APRIL that does not bind TACI or BCMA may not block the binding of TACI or BCMA to APRIL. The '694 patent, without providing specific antibodies, only generally refers to polyclonal and monoclonal antibodies that bind APRIL. That is, it cannot make any distinction between an antibody that does or does not block a TACI or BCMA receptor binding because it does not identify any receptors for APRIL. Thus, the Examiner has not shown that the alleged "inherent property" necessarily flows from the teachings of the '694 patent. Applicants do not believe that a basis for inherency has been established.

Third, claims 67-68 are not directed to all antibodies that bind APRIL, rather they are directed to a specific set of antibodies against APRIL that have special properties and characteristics that are not described in the '694 patent and are not of the same scope as the antibodies described in the '694 patent. Thus, a rejection based on inherent anticipation is not proper.

Finally, contrary to the Examiner's assertions, applicants have no burden to show that the antibodies of the '694 patent do not bind to APRIL because (1) the '694 patent does not inherently anticipate claims 67-68 for the above reasons and because (2) antibodies that generally bind APRIL are not the subject matter of the claims at issue.

In view of the foregoing, claims 67-68 are not anticipated by the '694 patent.

SUMMARY

The Examiner has indicated that claims 72-72, 74-75 and 77-78 and 80 are allowable. Applicants respectfully request that the Examiner withdraw his rejections and allow now pending claims 67-70, 73, 76, 79, 81-91 and added claims 95-96. If those claims are deemed allowable, applicants request that the Examiner reconsider withdraw claims 92-94 and added 97 for further examination. Applicants invite the Examiner to contact their representative by telephone to discuss any matter that would expedite the prosecution of the application.

In the unlikely event that this document is separated from the transmittal letter or if fees are required, applicants petition the Commissioner to authorize a charge to the Deposit Account 07-0630 for any fees required or credits due and any extensions of time necessary to maintain the pendency of this application.

Respectfully submitted,

GENENTECH, INC.

Date: December 2, 2003

By: _____

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